Management of Recurrent Non–Muscle Invasive Bladder Cancer

NYU Case of the Month, January 2018

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A 67-year-old man presented with a chief complaint of hematuria with clots. Urological workup performed at an outside institution included CT urogram, cystoscopy, cytology, and transurethral resection of the bladder tumor (TURBT), which revealed high-grade urothelial carcinoma with invasion into the lamina propria. No muscularis propria was present on the biopsy specimen. The patient was referred to NYU Langone Health for further management. Past medical history was significant for hypertension, hyperlipidemia, and a 30-pack/year history of smoking. His ECOG performance status was 0. He denied any significant lower urinary tract symptoms.

Relevant Prior History and Evaluation

- Hypertension
- Hyperlipidemia
- 30-pack/year smoking
- Right inguinal hernia repair

Physical Examination

- Abdomen: Soft, no palpable masses
- DRE: 50 gm, smooth, no nodules, non-fixed

Laboratory Results

- Cr: 0.9 mg/dL
- eGFR: 90 mL/min/1.73 m^2
- Hgb: 13.2 g/dL
- Hct: 40.3%
- PT: 11.6 seconds
- PTT: 26.9 seconds
- INR: 1.0
- UA: Moderate blood, negative nitrate, leukocyte esterase, protein
- PSA: 2.7 ng/mL

Imaging

CT urogram showed thickening and retraction along the right posterolateral bladder wall, involving the right ureterovesical junction and an additional focal area of slight asymmetrical nodularity and increased enhancement along the right superolateral bladder wall (Figure 1). There was also a

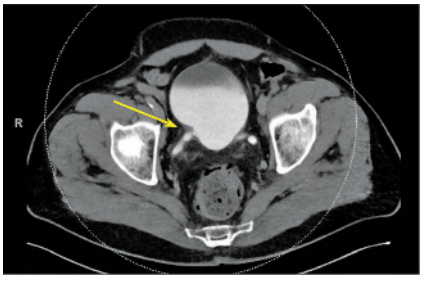

Figure 1. CT urogram demonstrating right bladder wall suspicious for urothelial carcinoma (*arrow*).

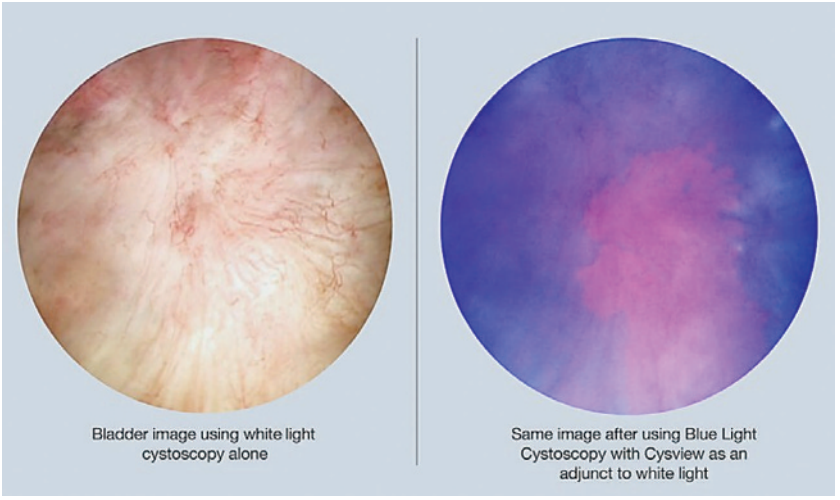

Figure 2. White light and blue light cystoscopy demonstrating tumor recurrence at the site of prior resection.

1.1-cm right common femoral node, slightly enlarged by size criteria but stable in size since 2013.

Management

Given the lack of muscularis propria in the resection specimen, the patient agreed to repeat TURBT with blue light cystoscopy, which found high-grade T1 urothelial carcinoma and carcinoma in situ (CIS) in the prior resection site (Figure 2). Muscularis propria was present and uninvolved. Both intravesical bacillus Calmette-Guérin (BCG) and radical cystoprostatectomy were discussed. The patient elected to proceed with a 6-week induction course of BCG. Surveillance cystoscopy at 6 months was unrevealing, although repeat cytology was positive for malignant cells. Further workup included repeat blue light cystoscopy and upper tract imaging. Repeat TURBT was positive for CIS (Figure 3), prostatic urethral biopsy was negative, and upper tract urine cytology was negative bilaterally.

The patient then underwent a re-induction course of BCG for 6 weeks, completing all treatments uneventfully. Surveillance cystoscopy at 6 months was again negative, but cytology remained positive. MRI urogram was negative. Repeat TURBT again demonstrated CIS in the posterior bladder wall. Given his BCG-refractory disease, the patient elected to undergo an early robotic radical cystectomy, extended pelvic lymphadenectomy, and intracorporeal neobladder (Figure 4). With our Enhanced Recovery after Surgery (ERAS) protocol, he was able to be discharged on postoperative day 4. A total of 57 lymph nodes were removed and final pathology revealed pT1N2M0+CIS.

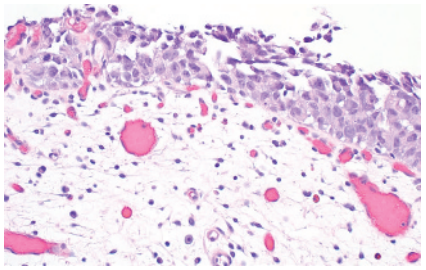

Figure 3. Urothelial carcinoma in situ. The urothelial cells demonstrate loss of polarity and enlarged, pleomorphic, and hyperchromatic nuclei with prominent nucleoli (H&E, 400x). Slide courtesy of Andrea R. Lightle, DO, Department of Pathology, NYU School of Medicine.

Surveillance imaging at 12 months demonstrated lymphadenopathy of the retroperitoneum consistent with recurrence. Given his excellent performance status, minimal comorbidities, and absence of visceral metastatic disease, he chose to enroll in a clinical trial of nivolumab (programmed cell death protein 1 [PD-1] inhibitor) plus NKTR-214 (pegylated IL-2) at NYU Langone.

Comment

Bladder carcinoma is the most common malignancy of the urinary tract. Up to 85% of patients with bladder cancer present with disease that is confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). Multiple factors are associated with bladder carcinogenesis; however, tobacco smoking is the most significant and most common risk factor. Reported estimates indicate that tobacco use is responsible for half of all cases; however, a lag time of 20 to 30 years is evident between cigarette exposure and diagnosis.[1]

Meticulous staging is imperative in bladder cancer to determine the appropriate treatment after initial TURBT. Thus, a repeat TURBT is recommended within 2 to 6 weeks in patients with a known

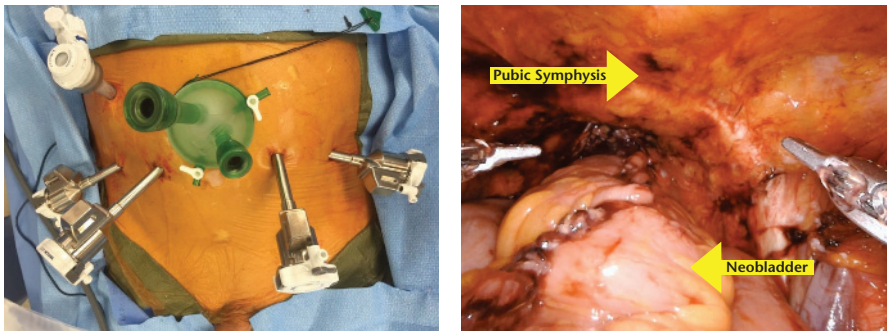

Figure 4. Robotic cystectomy with intracorporeal neobladder.

incompletely resected tumor or with tumors invading the lamina propria[2] independent of muscularis propria identified in the resected tissue. A randomized controlled trial has shown that repeat TURBT after newly diagnosed T1 bladder cancer improves recurrence-free survival and progression-free survival by 25% and 14%, respectively, at 5 years.[2] Incomplete resection is likely a significant contributing factor to early recurrences, as tumors have been noted at the first follow-up cystoscopic evaluation in up to 45% of patients.

CIS is a challenging entity to diagnose cystoscopically because these lesions are difficult to distinguish from normal bladder tissue. Instead, microscopic urinary analysis is required to identify atypical cells, and diagnosis is confirmed upon histological assessment of bladder tissue samples.

Cystoscopic detection of CIS may be enhanced by fluorescence cystoscopy.[2] At NYU Langone, we employ blue light cystoscopy, which improves the differentiation of lesions from normal tissue by taking advantage of the increased metabolic activity (blue light) that occurs in cancer cells and which has higher specificity for bladder cancers than traditional cystoscopy.

Risk stratification in concordance with guidelines is paramount for the optimal care of patients prior to each treatment decision. Our patient was classified as high risk given his T1 and CIS tumors. The American Urological Association/Society of Urologic Oncology Guideline defines high risk as high-grade Ta tumors >3 cm or multifocal, T1 tumor; multifocal, recurrent, and large (>3 cm) low-grade tumors; any CIS; BCG failure; lymphovascular invasion; variant histology; or prostatic urethral involvement.[2] Given the patient's high-risk disease, an induction course of BCG was given. In patients with a partial or no response, a second induction course of BCG is indicated.[2] Although BCG is a heterogeneous organism with at least eight different strains being used for intravesical therapy worldwide, there is insufficient evidence to recommend one strain or dose of BCG. T1 tumors have a high propensity to recur and progress to muscle invasion. Rates of upstaging to pT2 have been reported to occur in up to 41% of patients, and lymph node metastases are reportedly found in 13% at the time of radical cystectomy.[3]

At NYU Langone, we offer robotic cystectomy with intracorporeal orthotopic neobladder to suitable patients who do not want a stoma, have normal renal and liver functions, and are motivated to comply with neobladder training. In our experience, the robotic approach demonstrates equivalent oncological and functional outcomes with less blood loss and shorter hospital stays using our ERAS protocol compared with the open approach.[4]

With the known role of tumor immunity in urothelial carcinoma, along with the breakthrough success of immunotherapy agents, various checkpoint inhibitors are being evaluated in patients with metastatic urothelial carcinoma in both first-line and second-line settings.[5] Our patient chose to enroll in NYU protocol S16-02023 (NCT02983045), which is a multicenter trial of nivolumab (PD-1 inhibitor) plus NKTR- 214 (pegylated IL-2) as systemic therapy in patients with metastatic urothelial carcinoma being offered at NYU Langone. Surgeons are encouraged to learn more about these treatment options and to consider enrolling their patients in one of these potentially paradigm-changing clinical trials. ■

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